Original Article

Effect of combinations of dexamethasone-ondansetron and dexamethasone-ondansetron-aprepitant versus aprepitant alone for early postoperative nausea and vomiting after day care gynaecological laparoscopy: A randomised clinical trial

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ABSTRACT

Background and Aims: This study was designed to compare the effectiveness of the combination of dexamethasone–ondansetron with oral aprepitant alone and triple combination therapy with all three agents (dexamethasone-ondansetron and oral aprepitant) in the prevention of postoperative nausea and vomiting (PONV) in day care gynaecologic laparoscopy. **Methods:** This was a randomised clinical trial conducted at a university teaching hospital. A total of 105 female patients were randomised into the aprepitant (A), dexamethasone-ondansetron (DO) and aprepitant-dexamethasone-ondansetron (ADO) groups. The patients in the A group received only 80 mg oral aprepitant 1 h before surgery. The patients in the DO group, received dexamethasone 8 mg at induction with ondansetron 4 mg before extubation. Patients in the ADO group received 80 mg oral aprepitant 1 h before surgery, dexamethasone 8 mg at induction and ondansetron 4 mg before extubation. Incidence of nausea and vomiting was compared between groups using the Chi-square test/Fisher's test. Bellville score for severity of PONV was analysed using the Kruskall-Wallis test. *P* value < 0.05 was regarded as significant. **Results:** The incidence of PONV did not show a statistically significant difference between the three groups, with a *P* value of 0.13 (12.5%, 30.3% and 32.3% in groups ADO, DO and A, respectively). The severity of PONV measured using Bellville score was also not significantly different among the groups [median values (IQR) of 0 (0-0), 0 (0-1), and 0 (0-1)]. **Conclusion:** The combination of aprepitant, dexamethasone and ondansetron failed to demonstrate a statistically significant superiority over the other two antiemetic regimens.

Key words: Aprepitant, dexamethasone, ondansetron

INTRODUCTION

Aprepitant is a selective neurokinin-1 (NK-1) receptor antagonist. It is one of the various classes of drugs that can be used for the management of postoperative and post-discharge nausea and vomiting.[1] Dexamethasone is widely used in postoperative nausea and vomiting (PONV) and has minimal side effects with a single dose.[2,3] Ondansetron is a selective 5-hydroxy tryptamine 3(5-HT3) receptor antagonist which is useful in PONV.[4] However, despite many pharmacological strategies, PONV still remains a major problem especially after laparoscopies that necessitate prophylactic treatment.[5]

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Studies have shown that dexamethasone-ondansetron combination (OR = 0.42, 95% CI [0.20–0.90] $P = 0.02$) is better than ondansetron alone or dexamethasone alone in preventing PONV.[6] This study was designed to compare the effectiveness of the combination of dexamethasone-ondansetron with oral aprepitant alone and triple combination therapy with all three agents in the prevention of PONV in gynaecologic laparoscopy.

METHODS

The study was conducted from September 2018 to July 2019 in our hospital after obtaining approval from the Institute Ethics Committee and written, informed consent from all patients. We randomly allocated 105 female patients, 20–50 years, American Society of Anesthesiologists (ASA) 1 and 2, planned for day care gynaecological laparoscopy, into three groups. Randomisation was done using a computer-generated random number table, of varying block sizes. The master allocation schedule was kept in the central office of one of the investigators, while enrolment of participants was done by a second investigator and a third blinded investigator assigned participants to interventions. Concealment of group allocation was done using sequentially numbered opaque sealed envelopes.

The investigator who kept the master allocation schedule, was also responsible for drug preparation and distribution. The randomisation sequence was accessible only to this investigator. For each participant, study drugs for both intravenous (in 2-ml or 5-ml syringes containing dexamethasone, ondansetron or saline) and oral (aprepitant or placebo) administration were prepared and stored under supervision of the first investigator, with a shelf-life of one week under refrigerated conditions. A sealed opaque envelope containing the study allocation was also prepared by the first investigator to accompany the patient during study drug administration and facilitate rapid unblinding if required urgently. Syringes were labelled with a unique study identification number and expiry date, placed in a single pack along with the oral drug (or placebo) with the unblinding envelope and transferred to a suitable storage location. The allocation sequence and block size were only known to the first investigator and remained concealed from the other investigators until the final patient had completed the follow-up.

Patients with prior cardiovascular, respiratory, or gastrointestinal diseases, diabetics, those with previous history of PONV or nausea and vomiting due to any reason, preoperative use of antiemetics or opioids, pregnant women, allergy to any of the drugs under study and inadequate nil per oral (NPO) status were excluded. The study groups were: Group A, administered 80 mg oral aprepitant capsule 1 hour before operation along with 2 ml and 5 ml intravenous (IV) saline at induction and at the end of surgery respectively; Group DO, administered placebo, matched to oral aprepitant capsule, 1 h before the operation, 8 mg dexamethasone at induction and 4 mg ondansetron at the end of surgery; and Group ADO, administered 80 mg oral aprepitant capsule 1 h before the operation, 8 mg dexamethasone at induction and 4 mg ondansetron at the end of surgery.

The dose of oral aprepitant was decided upon by consensus among the investigators following an objective assessment of the probability of PONV, based on the number of the independent risk factors, as has been described by earlier authors.[7,8] It was projected that the PONV probability among our patients would be of the order of 60–70%.[9] It was therefore decided to opt for a dose of 80 mg of oral aprepitant, as this has been shown to be effective in patients at higher risk of PONV.[10-12]

The preoperative examination was done on the morning of proposed surgery. Adequate nil per oral status was confirmed. After entrance into the operating room, heart rate (HR), non-invasive blood pressure (NIBP), and oxygen saturation (SaO_2) were recorded. IV line was established. Anaesthesia was induced with 1 mg midazolam, 2 μg/kg fentanyl, 2-3 mg/kg propofol, 0.5 mg/kg atracurium and Proseal laryngeal mask airway (LMA), number 3 or 4 was placed. Group DO and ADO patients received inj. dexamethasone 8 mg IV and group A patients received 2 ml saline immediately after induction.

Sevoflurane was used for maintenance of anaesthesia with minimum alveolar concentration (MAC) 1.0–1.3 in air-oxygen mixture. Patients were ventilated with tidal volume 7–10 ml/kg and frequency of 10–12 per minute. Intraoperative vital signs such as HR, NIBP (every 3 min), electrocardiogram (ECG) lead II and end-tidal carbon dioxide ($EtCO_2$) were recorded.

Group DO and ADO patients received inj. ondansetron 4 mg IV and group A patients, 5 ml saline at the end

of surgery during placement of skin sutures on the laparoscopy ports. Following adequate recovery, LMA was removed according to standard extubation criteria after reversal of neuromuscular blockade, and the patient transferred to the post-anaesthesia care unit (PACU).

In PACU, patients were observed for nausea and vomiting hourly up to 4 h and if any such episode occurred, its severity was measured with the Bellville score (0 = without nausea and vomiting, 1 = sense of nausea, 2 = sense of nausea with belching, 3 = having vomiting). For a Bellville score of 2 or 3, metoclopramide 10 mg IV was infused slowly. Nausea and vomiting, metoclopramide administration, other complications such as pain (Visual Analogue Score, VAS < or ≥4), agitation (present or absent), lethargy (present or absent) and basic vital signs were recorded. Time to discharge of patients was also noted. All patients were blinded to the group allocation. Data were collected by a blinded assessor. The primary outcome measure was the incidence of nausea and/or vomiting in the first 4 h following surgery. The secondary outcome measures included the severity of symptoms and side effect profiles of drugs. Postoperative analgesia was provided with inj. paracetamol 1 g for all patients, with boluses of fentanyl 0.5 μg/kg for VAS score exceeding 4 as often as required. However, some patients who demanded repeated doses of fentanyl, were offered morphine or tramadol. The total number of patients in each group that received any of these opioids as rescue analgesia, was recorded.

The sample size was estimated using nMaster-2.0 software as $n = 105$ ($n = 35$ in each group) to have a 95% chance with a one-sided test of detecting 30% reduction in early PONV with triple antiemetic group, and within group standard deviation of 0.4, when compared to dexamethasone-ondansetron and aprepitant group with 80% power and with an expectation of 10% dropouts. The sample size was determined *a priori* using the statistical formula for comparing the incidence of PONV among the groups based on previous studies by Diemunsch P *et al*.[13] and de Morais LC *et al*.[14] and Maddali MM *et al*.[15].

The primary parameters assessed were the incidence and severity of PONV among the groups.

The statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software version 20.0 [Armonk, NY: International Business Machines (IBM) Corp.] and WPS Office Excel and Word were used to design the table and graphical data. The distribution of categorical variables such as nausea, vomiting, need for rescue antiemetics, pain, agitation, lethargy, use of opioids, ASA physical status, etc., were expressed in terms of frequency (number) and percentage (%). The comparison of these categorical variables between the groups was carried out by using the Chi-square test/Fisher's test as relevant.

The distribution of continuous variables such as age, weight, and duration of surgery, was expressed in terms of the median with an interquartile range based on the non-normal distribution of data as estimated by Kolmogorov-Smirnov test of normality. The comparison of these continuous and discrete variables was done using the Mann-Whitney test. The comparison of ordinal data such as Bellville score ranging from 0 to 3 for estimating the severity of nausea and vomiting was expressed as median with interquartile range (IQR) and analysed using the Kruskall-Wallis test. All statistical analysis was performed at 5% level of significance.

P value <0.05 was regarded as significant to reject the null hypothesis.

RESULTS

Of the 105 women allocated into the three groups, 96 women were eventually analysed [Figure 1]. Patient demographic data and durations of surgery are shown in Table 1.

The incidence of PONV in the first 4 hours following surgery was 25%. In group ADO, 12.5% patients had nausea and/or vomiting. Totally, 3.1% of these patients had at least one episode of vomiting.

The corresponding incidences of PONV in groups DO and A were 30.3% and 32.3%, respectively. Similarly, the incidence of vomiting in these two groups was 3% and 9.7%, respectively. Table 2 shows that the incidence of PONV in group ADO, was not statistically significantly different from groups A and DO.

The severity of nausea and vomiting, measured using the Bellville score, was non-normal data. This was expressed as median (IQR). Table 3 shows the severity of PONV which was comparable among the groups. When the Bellville score was ≥2, inj. metoclopramide 10 mg was given as rescue treatment in 4 (12.5%), 6 (18.2%), and 7 (22.6%) of patients in groups ADO, DO, and A, respectively. Table 3 also shows the need

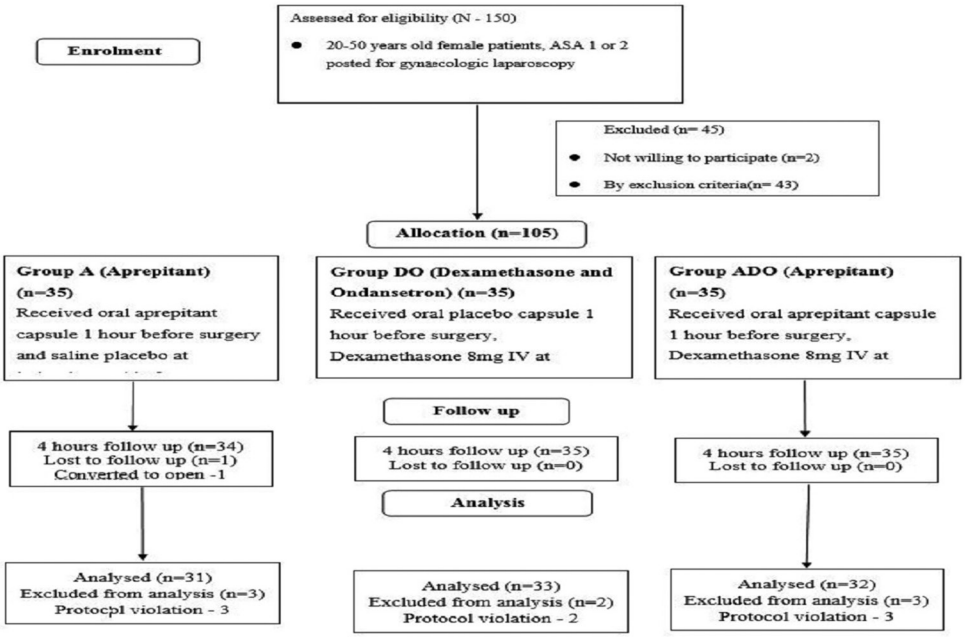

Figure 1: CONSORT flow diagram showing patient progress through the study phases

Table 1: Patient demographic characteristics and surgical durations

Parameter	Group A (*n*=31)	Group DO (*n*=33)	Group ADO (*n*=32)	*P*
Age (years) [median (IQR)]	27 (25-31)	28 (26-32.5)	27 (25-30)	
Weight (kg) [median (IQR)]	57 (50-60)	65 (54.5-72.5)	57.5 (50-60)	
ASA PS class (I/II) [n (%)]	25/6 (80.6/19.4)	31/2 (93.9/6.1)	28/4 (87.1/12.9)	
Duration of surgery (minutes) [median (IQR)]	60 (45-75)	60 (45-97.5)	60 (60-120)	0.02*
Type of surgery				
Laparoscopic cystectomy	4 (4.16%)	8 (8.33%)	7 (7.29%)	
Diagnostic hysterolaparoscopy	7 (7.29%)	6 (6.25%)	11 (11.45%)	
Laparoscopic sterilisation	20 (20.83%)	19 (19.79%)	14 (14.58%)	

IQR, Inter-quartile range; ASA PS, American Society of Anesthesiologists' Physical Status

for rescue treatment which was comparable among the groups.

VAS scores for pain >4 could affect the assessment of severity of PONV. The VAS scores were recorded as dichotomous variables with VAS ≤4 or VAS >4 being comparable between the groups. Postoperative adverse effects which might have altered the assessment of PONV, like pain, agitation, and lethargy, assessed within the first four hours were comparable among the groups. No patient experienced agitation or lethargy. One patient had delirium that lasted for 5–10 min in group A.

The times to discharge were not significantly different between the three groups (group A = 7.2 ± 1, group DO 7.3 ± 7.4, and group ADO = 7.5 ± 0.8 h. $P = 0.43$).

DISCUSSION

In this study, the overall incidence of PONV in the first 4 h following surgery was 25%. All the patients included in the study had 2–3 risk factors for PONV. Previous studies conclude that incidence of PONV among such patients is 60–80% without antiemetic prophylaxis.[16-18] The reduction in the PONV incidence to 25% in the study is attributable to the prophylactic antiemetics used. The incidence of PONV in patients undergoing gynaecological laparoscopy for 4 h after surgery was found to be 12.5% in ADO group, 30.3% in DO group and 32.2% in group A. Adding aprepitant to dexamethasone-ondansetron, did not statistically significantly reduce the incidence of PONV, as compared to other groups that were administered aprepitant

Table 2: Comparison of frequency of PONV between the groups

Parameter	Group A (*n*=31)	Group DO (*n*=33)	Group ADO (*n*=32)	*P*
PONV (0-4 h) [*n* (%)]	10 (32.3%)	10 (30.3%)	4 (12.5%)	0.13
Nausea (0-4 h) [*n* (%)]	7 (22.6%)	9 (27.3%)	3 (9.4%)	0.17
Vomiting (0-4 h) [*n* (%)]	3 (9.7%)	1 (3%)	1 (3.1%)	0.40

PONV, Postoperative Nausea and Vomiting

Table 3: Comparison of severity of PONV and VAS scores

Parameter	Group A (*n*=31)	Group DO (*n*=33)	Group ADO (*n*=32)	*P*
Bellville score (0-4 h) [median (IQR)]	0 (0-1)	0 (0-1)	0 (0-0)	0.17
Rescue antiemetics [*n* (%)]	7 (22.6%)	6 (18.2%)	4 (12.5%)	0.58
VAS (0-4 h) (>4) [*n* (%)]	21 (70%)	21 (67.7%)	13 (44.8%)	0.09

IQR, Inter-quartile range; VAS, Visual Analogue Score, PONV, Postoperative nausea and vomiting

alone or were given dexamethasone-ondansetron combinations.

Some studies have shown that combination therapy with multiple antiemetics is better than single/double antiemetic prophylactic therapy.[5,9] However, Hache *et al*. studied the incidence of PONV among high risk patients and found that the incidence of PONV was similar whether aprepitant was combined with one or two antiemetics and that the incidence of PONV paradoxically increased when aprepitant was combined with 3 or 4 antiemetics.[19] Similarly, another study showed that oral aprepitant has comparable effects to ondansetron in reducing the incidence of PONV, the severity of nausea, number of rescue antiemetics, and the time to first emetic episode in the first 24 h postoperative period.[20] In our study, we found that while the incidence of PONV was reduced from 60–80% to 30% with 2 antiemetics, adding aprepitant did not further reduce the incidence of PONV by a margin sufficient to attain statistical significance. We also found that a single dose of aprepitant alone was as efficacious as 2 or 3 antiemetics. This finding is in accordance with some studies which have shown that a single antiemetic is as efficacious as combination therapy especially when the antiemetic is a potent one like aprepitant. Green *et al*. have found that aprepitant is as efficacious as a combination of aprepitant with transdermal scopolamine, in preventing PONV in patients undergoing elective surgical procedures lasting more than 60 min under general anaesthesia.[21] In another study, 40 mg aprepitant was found to be better than multimodal therapy in preventing PONV in patients receiving extended-release epidural morphine for postoperative analgesia.[22] The severity of nausea and vomiting was assessed using Bellville score in our study. This is a standard clinical scoring system for assessment of the severity of nausea and vomiting.[23] It includes 0 for lack of nausea and vomiting, 1 for nausea, 2 for nausea with belching, and 3 for vomiting. The medians with IQR of Bellville score were 0 (0–1), 0 (0–1), and 0 (0–0) in A group, DO group and ADO group, respectively. There was no statistically significant difference in the severity of PONV among the groups.

In our study, metoclopramide was given as rescue antiemetic to those patients with Bellville score of > 2. The use of rescue antiemetics was also comparable among the groups A, DO, and ADO, respectively. Postoperative adverse effects which may have altered the assessment of PONV like pain, agitation, and lethargy, assessed in the first four hours were comparable among the groups with no patient experiencing agitation or lethargy, and one patient having delirium lasting for 5–10 min in group A. VAS scores for pain were comparable among the groups with no statistical significance (*P* value – 0.09). Eleven out of 96 patients received opioids like fentanyl, morphine and tramadol for analgesia. These included 3 (9.4%) patients in group ADO, 5 (15.2%) in group DO and 3 (9.7%) in group A. The number of patients who received opioids were comparable among the groups. Hence, giving opioids did not affect the outcome and the outcome was dependent on the antiemetic drugs, although admittedly, that the type of opioid used, could have been a confounder in this regard.

The limitations of this study include the fact that confounding factors like the duration and type of surgery could have affected the outcomes. The type of surgeries extended from laparoscopic sterilisation with minimal manipulation and duration lasting less than 60 min to hysterolaparoscopy or laparoscopic ovarian cystectomy with more manipulation compared to laparoscopic sterilisation and duration lasting up to a maximum of 210 min. This could have influenced the outcomes. The cost-effectiveness of prophylactic antiemetics was not assessed which could have helped in determining the most cost-effective antiemetic prophylactic regimen. We did not collect data of post-discharge nausea and vomiting which could have added on to the assessment of PONV since the study assessment was done in the first four hours in the PACU only and did not include follow-up following discharge there from. Finally, we did not analyse rescue analgesia with opioids based on the emetic potential of individual opioids, but merely compared the number of patients receiving opioids for individual groups, which could be viewed as another weakness of the study.

CONCLUSION

In conclusion, in this study, we found that the combination of aprepitant, dexamethasone and

ondansetron failed to demonstrate any superiority in comparison to aprepitant administered alone, or dexamethasone-ondansetron combination, with respect to the incidence or severity of early PONV following day care gynaecological laparoscopy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kulkarni S, Harsoor SS, Chandrasekar M, Bhaskar SB, Bapat J, Ramdas EK, *et al*. Consensus statement on anaesthesia for day care surgeries. Indian J Anaesth 2017;61:110-24.
2. Erhan Y, Erhan E, Aydede H, Yumus O, Yentur A. Ondansetron, granisetron, and dexamethasone compared for the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: A randomized placebo-controlled study. Surg Endosc 2008;22:1487–92.
3. D'souza N, Swami M, Bhagwat S. Comparative study of dexamethasone and ondansetron for prophylaxis of postoperative nausea and vomiting in laparoscopic gynecologic surgery. Int J Gynecol Obstet 2011;113:124–7.
4. Wang XX, Zhou Q, Pan DB, Deng HW, Zhou AG, Huang FR, *et al*. Dexamethasone versus ondansetron in the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic surgery: A meta-analysis of randomized controlled trials. BMC Anesthesiol 2015;15:118.
5. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, *et al*. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004;350:2441-51.
6. Awad K, Ahmed H, Abushouk AI, Al Nahrawi S, Elsherbeny MY, Mustafa SM, *et al*. Dexamethasone combined with other antiemetics versus single antiemetics for prevention of postoperative nausea and vomiting after laparoscopic cholecystectomy: An updated systematic review and meta-analysis. Int J Surg 2016;36:152–63.
7. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: Conclusions from cross-validations between two centers. Anesthesiology 1999;91:693-700.
8. Li J, Ye H, Shen W, Chen Q, Lin Y, Gan X. Retrospective analysis of risk factors of postoperative nausea and vomiting in patients undergoing ambulatory strabismus surgery via general anaesthesia. Indian J Anaesth 2020;64:375-82.
9. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, *et al*. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014;118:85-113.
10. Kakuta N, Tsutsumi YM, Horikawa YT, Kawano H, Kinoshita M, Tanaka K, *et al.* Neurokinin-1 receptor antagonism, aprepitant, effectively diminishes post-operative nausea and vomiting while increasing analgesic tolerance in laparoscopic gynecological procedures. J Med Invest 2011;58:246–51.
11. Jung WS, Kim YB, Park HY, Choi WJ, Yang HS. Oral administration of aprepitant to prevent postoperative nausea in highly susceptible patients after gynecological laparoscopy. J Anesth 2013;27:396–401.
12. Singh PM, Borle A, Rewari V, Makkar JK, Trikha A, Sinha AC, *et al.* Aprepitant for postoperative nausea and vomiting: A systematic review and meta-analysis. Postgrad Med J 2016;92:87–98.
13. Diemunsch P, Joshi GP, Brichant JF. Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting. Br J Anaesth 2009;103:7–13.
14. de Morais LC, Sousa AM, Flora GF, Grigio TR, Guimarães GMN, Ashmawi HA. Aprepitant as a fourth antiemetic prophylactic strategy in high-risk patients: A double-blind, randomized trial. Acta Anaesthesiol Scand 2018;62:483–92.
15. Maddali MM, Mathew J, Fahr J, Zarroug AW. Postoperative nausea and vomiting in diagnostic gynaecological laparoscopic procedures: Comparison of the efficacy of the combination of dexamethasone and metoclopramide with that of dexamethasone and ondansetron. J Postgrad Med 2003;49:302-6.
16. Bergese S, Viloria A, Uribe A, Antor A, Fernandez S. Aprepitant versus ondansetron in preoperative triple-therapy treatment of nausea and vomiting in neurosurgery patients: Study protocol for a randomized controlled trial. Trials 2012;13:130.
17. Rüsch D, Eberhart LHJ, Wallenborn J, Kranke P. Nausea and vomiting after surgery under general anesthesia —an evidence-based review concerning risk assessment, prevention, and treatment. Dtsch Arztebl Int 2010;107:733–41.
18. Fisher DM. The "Big Little Problem" of postoperative nausea and vomiting: Do we know the answer yet? Anesthesiology 1997;87:1271–3.
19. Hache JJ, Vallejo MC, Waters JH, Williams BA. Aprepitant in a multimodal approach for prevention of postoperative nausea and vomiting in high-risk patients: Is there such a thing as "Too Many Modalities"? Sci World J 2009;9:291–9.
20. Jeyabalan S, Thampi SM, Karuppusami R, Samuel K. Comparing the efficacy of aprepitant and ondansetron for the prevention of postoperative nausea and vomiting (PONV): A double blinded, randomised control trial in patients undergoing breast and thyroid surgeries. Indian J Anaesth 2019;63:289-94.
21. Green MS, Green P, Malayaman SN, Hepler M, Neubert LJ, Horrow JC. Randomized, double-blind comparison of oral aprepitant alone compared with aprepitant and transdermal scopolamine for prevention of postoperative nausea and vomiting. Br J Anaesth 2012;109:716–22.
22. Hartrick CT, Tang YS, Hunstad D, Pappas J, Muir K, Pestano C, *et al*. Aprepitant vs. multimodal prophylaxis in the prevention of nausea and vomiting following extended-release epidural morphine. Pain Pract 2010;10:245–8.
23. Bellville JW, Bross ID, Howland WS. A method for the clinical evaluation of antiemetic agents. Anesthesiology 1959;20:753–60.